REMARKS

Claims 24, 26, and 28-32 are currently pending in the application. No new matter is added.

At the outset, Applicants would like to thank Examiner Zeman for taking the time to discuss the outstanding rejections with Applicant's representatives on March 13, 2007. The substantive points discussed during the interview are incorporated into the current remarks.

Rejection of Claims 24, 26, and 28-32 Under 35 U.S.C. §103(a)

Kullberg et al.

The Office Action rejected claims 24, 26, and 28-32 under 35 U.S.C. §103 as being unpatentable over Kullberg et al. (J. Immunology, 1992, 148:3264). The Office Action asserts that Kullberg et al. teach that the helminthic parasite *Schistosoma mansoni* down regulates the Th1 cytokine secretion of IL-2 and IFN-γ in mice, and that Th1 responses were determined by cytokine profiles as measured by *in vitro* ELISA assays. The Office Action states that Kullberg et al. differ from the claimed invention in that they do not teach steps of fractionating, sub-fractionating and testing of the sub-fractions. The Office Action asserts that, since methods of fractionation and sub-fractionation are well known and routine, one of skill in the art would have been motivated to use such methods to identify the component of the parasite composition responsible for downregulation of Th1 cytokine secretion as taught by Kullberg et al. The Office Action asserts that one of skill in the art would have been motivated to identify the components in order to produce a "pure" composition capable of reducing a Th1 response without possible negative effects caused by the other constituents of the nematode composition. Applicants respectfully disagree and traverse the rejection.

Regardless of whether the technique of fractionating and sub-fractionating a helminthic parasite preparation were well known or routine at the time of the instant invention, one of skill in the art, based on the disclosure of Kullberg et al., would not have been motivated to screen a helminthic parasite preparation in search of a component that reduces a Th1 immune response. It is clear law that the mere fact that a device or process utilizes known scientific principle does not

alone make that device or process obvious. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044 (Fed. Cir. 1988). Kullberg et al. describe *S. mansoni* infected mice as a model system useful for determining altered antibody and cytokine production in response to non-parasite antigen. Indeed, Kullberg et al. refer to the infected mice merely as a "murine *S. mansoni* model", useful to determine immune response to non-parasite antigen (p. 3269, col. 2., last paragraph). The teachings of Kullberg et al. are focused specifically on addressing "the question of whether the in vivo environment in infected animals may influence the outcome of a developing immune response to another foreign Ag" (p. 3264, second column). Kullberg et al. does not teach or even suggest using the murine *S. mansoni* model to determine what component of the helminth infection is causing the changes in antibody and/or cytokine production, but instead, is focused on the immune response itself. In fact, Kullberg et al. points to the future directions in which the study could evolve: "the results presented here may have implications for intercurrent infections or immunizations during human *S. mansoni* infection" (p. 3269). Again, Kullberg et al. is focused on the immune response in a model of helminth infection, and makes no suggestion to determine the component of the helminth that is responsible for causing the altered immune response.

At best the teachings of Kullberg et al. may render the instant invention obvious to try, which is not sufficient to support a finding of obviousness. The Federal Circuit has long held that "obvious to try" does not constitute "obviousness." The court in In re O'Farrell (853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988)) made an excellent distinction between these two concepts. Judge Rich noted that "[a]ny invention that would in fact have been obvious under §103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious?" (*Id.* at pages 1680-81). He went on to state that

> The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *[4 case cites omitted]*. In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where

> the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

(*Id.*, at 1681). The instant rejection under §103, falls into Judge Rich's second category. The entire focus of the Kullberg et al. reference is to study the immune response, specifically cytokine and antibody production, to antigen in a murine *S. mansoni* model. There is no disclosure in Kullberg et al. that would motivate one of skill in the art to completely shift the analysis described by Kullberg et al. from a study of the character of an immune response to non-parasite antigen, to an entirely new field of experimentation (neither taught or suggested by Kullberg et al.) to attempt to identify an active component of the helminth. Kullberg et al. already provides a working animal model in which to study the immune system, and does not contain any teachings that would suggest to one of skill in the art to study the etiology of the mouse model itself to determine whether a component of the helminth was responsible for the changed immune response. Thus, one of skill in the art, regardless of how routine the technical steps of fractionation and sub-fractionation are, would not have been motivated to endeavor to identify an active fraction of *S. mansoni* because there is no teaching in Kullberg et al. to seek out a component of the helminth that causes altered cytokine and/or antibody production. The only guidance provided by Kullberg et al. regarding future experimentation is the implication that infected humans may have altered cell mediated immune function to other microbial agents, thus, suggesting further research into concurrent infection. This is insufficient to motivate one of skill in the art to deviate completely from the scope of Kullberg et al. as suggested by the Office Action. The pending claims are therefore non-obvious over the teachings of Kullberg et al. and Applicants request that the rejection be reconsidered and withdrawn.

Lee et al.

The Office Action also rejected claims 24, 26, and 28-32 as unpatentable over Lee et al. (WO 96/29802). The Office Action asserts that Lee et al. teach the down regulation of Th1 activity in mice can be accomplished by administration of a soluble helminthic nematode extract. The Office Action states that Lee et al. do not teach the steps of fractionation, sub-fractionation, and sub-fraction testing. The Office Action asserts that, since methods of fractionation and sub-fractionation are well known and routine, one of skill in the art would have been motivated to use

such methods to identify the component of the parasite composition responsible for downregulation of Th1 cytokine secretion as taught by Lee et al. The Office Action asserts that one of skill in the art would have been motivated to identify the components in order to produce a "pure" composition capable of reducing a Th1 response without possible negative effects caused by the other constituents of the nematode composition. Applicants respectfully disagree.

Regardless of whether the technique of fractionating and sub-fractionating a helminthic parasite preparation were well known at the time of the instant invention, one of skill in the art, based on the disclosure of Lee et al. would not have been motivated to screen a helminthic parasite preparation in search of a component that reduces a Th1 immune response.

It is well settled law that even when a finding of obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference. See, *B.F. Goodrich Co. v. Aircraft Breaking Sys. Corp.*, 72 F.3d 1577, 1582 (Fed. Cir. 1997). In addition, the showing of motivation must be clear and particular; broad conclusory statements about the teaching are not evidence of motivation. See, *In re Dembiczak*, 175 F.3d 994, 1000 (Fed. Cir. 1999). There is no teaching or even a suggestion by Lee et al. to fractionate a helminthic preparation, assaying a fraction to determine whether the fraction decreases a Th1 immune response, further fractionate the initial fraction, and then assay the sub-fraction to identify a sub-fraction that reduces a Th1 immune response.

Despite referring to the composition used as an "extract," a review of the working example provided by Lee et al. shows that the experiments were performed with a helminthic homogenate, not an extract (p. 8, line 2). Regardless, while live helminthic parasite infection increased kidney allograft survival in mice, the results shown in Table 1 show that the nematode homogenate was less effective than the whole worm infection in prolonging allograft survival. Thus, in addition to the complete absence of any guidance or suggestion in Lee et al. to identify a component of the helminth, the data in Lee et al. suggests that live worm infection gives the best results. Therefore, one of skill in the art would not have been motivated, given the teachings of Lee et al., to experiment, unguided, in a direction that even more greatly diverges from a system (i.e., whole nematode infection) that Lee et al teaches provides the more superior allograft

survival time. Based on the Lee et al. data, one of skill in the art could have concluded that there was something unique about whole worm infection that provided better results and, thus, would not have been motivated to move away from the teachings of Lee et al. to attempt to identify a single component of the helminth that reduces Th1 responses. Moreover, given that the worm homogenate produced poorer results than whole nematode infection, one of skill in the art would not have reasonably expected to be successful in identifying a component that reduced Th1 immune responses, since Lee et al. teaches that allograft survival decreases as you move away from whole worm infection (i.e., by using a homogenate).

It is clear law that the mere fact that a device or process utilizes known scientific principle does not alone make that device or process obvious. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044 (Fed. Cir. 1988). In this case, the mere fact that fractionation was technically feasible would not have motivated one of skill in the art to modify the teachings of Lee et al., particularly where Lee et al. report better allograft survival rates using active, live helminth infection. There is simply no teaching or suggestion in Lee et al. that would motivate one of skill in the art to perform the steps required by the instant claims.

Furthermore, the teachings of Lee et al. would teach away from the combination suggested by the Office Action. It is well settled that a reference may be said to teach away "when a person or ordinary skill, upon reading the reference would... be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994). It is also well established that "a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Id.* The data shown in Table 1 of Lee et al. teaches that allograft survival was diminished following extract administration relative to live worm infection. Thus, one of skill in the art would interpret such results as suggesting that further purification of a helminthic parasite preparation would be unlikely to produce the result sought by the instant claims. Claims 24, 26, and 28-32 are, therefore, non-obvious over the teachings of Lee et al., and Applicants request that the rejection be reconsidered and withdrawn.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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